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| 10/568,806 | 10/03/2008 | Daniel Harari | HARARI 1 | 7157 |

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| EXAMINER | |
|---|---|
| XIE, XIAOZHEN | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/568,806 | HARARI, DANIEL | |
| | Examiner | Art Unit | |
| | XIAOZHEN XIE | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4,5 and 8-41* is/are pending in the application.

4a) Of the above claim(s) *5,15-31 and 33-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,8-14,32 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 February 2006 and 25 October 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20101025*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendment*

The Information Disclosure Statement (IDS) filed 25 October 2010 has been entered. Applicant's submission of the replacement drawings filed 25 October 2010 is acknowledged. Applicant's amendments of the specification and the claims filed 25 October 2010 have been entered. Applicant's remarks filed 25 October 2010 are acknowledged.

### *Election/Restrictions*

The previous Office Action indicates that "Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a))." Applicant argues that Applicant did in fact make specific criticisms of the restriction requirement, i.e., that the restriction requirement did not make it clear whether it was a requirement for election of species or not. In view of the clarification of the Restriction Requirement set forth in the previous Office Action that the election of one splicing variant is not a species election, but a distinct invention, Applicant traverses that the different claimed splicing variants are related, while maintaining the prior election.

Applicant argues that the PCT rules do allow for examination of multiple products when there is "a technical relationship among those inventions involving one or more of the same or corresponding technical features." (PCT Rule 13.2) There is "no [unity] problem in the case of a genus/species situation where the genus claim avoids

the prior art", even though multiple species are claimed. (PCT Administrative Instructions, Annex B, paragraph (c) (i)) Applicant argues that the splicing variants recited in claim 1 are constrained to Class I (referring to Table 4), thus, Class I splicing variants for ErbB ligands qualifies as a genus. Applicant argues that while the sequences are different, that does not establish that they are unrelated.

Applicants' argument has been fully considered but has not been found to be persuasive.

As set forth previously, the polypeptides of Group I, represented by different SEQ ID NOs, are drawn to multiple distinct products which have different structures and functions. For example, the amino acid sequences shown in the SEQ ID NOs represent splicing variants for different ErbB family ligands, such as EGF, HB-EGF, NGR, etc. These molecules not only differ in the amino acid sequences, but they are derived from structurally and functionally distinct ErbB family ligand genes. Applicant argues that the splicing variants recited in claim 1 are constrained to Class I and they belong to the genus of Class I splicing variants for ErbB ligands. However, the Class I variants denoted by Applicant are "sequences found in the EST, NR and patent (DNA) databases having sequence encoding ErbB ligand variants comprising an elongated Exon A, resulting in protein sequence truncated after the conserved cysteine-4 of the EGF domain" (pp. 30, Table 2). The listed Class I variants include different gene products, as well as the translation products of EST sequences (partial gene products). Each of the Class I variants has a different exon sequence. Further, the claimed splicing variants have a materially different design, mode of operation, function, or effect. They

do not overlap in scope, i.e., are mutually exclusive; and there is nothing of record to show them to be obvious variants. Thus, each of the products is drawn to a distinct invention because they lack the same or corresponding technical feature.

For these reasons, the requirement is still deemed proper and is therefore made FINAL. Claim 2, 3, 6 and 7 are cancelled. Claim 41 has been added. Claims 1, 4, 5 and 8-41 are pending. Claims 5, 15-31 and 33-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 1, 4, 8-14, 32 and 41 are under examination to the extent they read on the elected invention of splicing variant SEQ ID NO: 81.

### *Drawings*

The objection to the drawings (specifically, Figures 1, 2, 3, 4, 5B and 6) under 37 CFR 1.83(a) as failing to show details as described in the specification is withdrawn in response to Applicant's submission of the replacement drawings filed on 25 October 2010.

### *Specification*

The objection to the specification for not including, as a first paragraph, a claim to benefit of priority to provisional Application No. 60/495,898, is withdrawn in response to Applicant's argument that the domestic priority information is presented in the ADS, and 37 CFR 1.76(a)(5) states that it need not be made part of the specification.

The objection to the specification for containing an embedded hyperlink and/or other form of browser-executable code is withdrawn in response to Applicant's amendment of the specification.

***Claim Rejections Withdrawn***

The rejection of claims 1-14 under 35 U.S.C. § 101 as the claimed invention drawn to non-statutory subject matter, is withdrawn in response to Applicant's amendment of the independent claim 1 to recite "*an isolated polypeptide*".

The rejection of claims 1-3, 6, 8-14 and 32 under 35 U.S.C. 102(b), as being anticipated by Eppenberger et al. (WO 99/14323), is withdrawn in response to Applicant's amendment of claims to limit the splice variant of an ErbB ligand as with the amino acid sequence of any one of SEQ ID NOs: 74-84, 93, 95-104 and 109-110. None of the above amino acid sequences is derived from HRG (also known as NRG1) that is taught in the Eppenberger et al. disclosure; and the claims have been amended to exclude the reference to the HRG splice variant (SEQ ID NO: 73).

The rejection of claims 1, 2, 4, 6 and 8-14 under 35 U.S.C. 102(b), as being anticipated by Loukianov et al. (Gene, 1997, Vol. 195(1):81-86), is withdrawn in response to Applicant's amendment of claims to limit "*wherein the fourth cysteine in said truncated EGF domain is the penultimate amino acid at the C-terminus of the polypeptide*". The SF HB-EGF polypeptide taught by Loukianov et al. has a 9 amino acid tail after the fourth cysteine.

***Claim Objections***

Claims 8 and 9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 8 and 9 recite "*wherein the splice variant has at least 90% (or at least 95%) homology to the aligned amino acid sequence of the same fragment in the EGF domain of a known ErbB ligand between cysteine I and cysteine 4*". However, the previous claim 1 limits "*a splice variant of an ErbB ligand with the sequence set forth in any one of SEQ ID NOS: 74-84, 93, 95-104, or 109-110*", which does not encompass homologous variants of the recited SEQ IDs. Thus, the claims fail to further limit the subject matter of the previous claim.

Claims 1 and 4 are objected to because of the following informalities: claims 1 and 4 recite non-elected invention. Applicant has elected SEQ ID NO: 81 as the one splice variant of an ErbB ligand in the response filed 7 May 2010. As discussed above, the polypeptides represented by different SEQ ID NOs are drawn to multiple distinct products that lack the same or corresponding technical feature. The PCT rules do not provide for the examination of multiple products in one application.

Claim 1 is objected to because of the following informalities: claim 1 recites "*with the sequence set forth in any one of …95-104 or 109-110*", which should be "and".

### *Claim Rejections Maintained*

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 8-14, 32 and 41 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, for reasons set forth in the previous Office Action and the following.

Applicant argues that the amended set of claims overcomes this rejection, as it is limited to specific sequences (class I variants).

Applicants' argument has been fully considered but has not been found to be persuasive.

Independent claim 1 has been amended to recite "*An isolated polypeptide comprising a splice variant of an ErbB ligand with the sequence set forth in any one of SEQ ID NOs:74-84, 93, 95-104, or 109-110, wherein the splice variant of an ErbB ligand is encoded by differential exon usage comprising a truncated EGF domain having only the first four of the six conserved cysteines found in an intact EGF domain, and wherein the fourth cysteine in said truncated EGF domain is the penultimate amino acid at the C terminus of the polypeptide.*" Depending claim 10 further recites "*The polypeptide of claim 1 wherein the N terminal flanking sequences preceding the cysteine 1 are at least 90% homologous to the same sequence in the EGF domain of a known ErbB ligand.*" The claims as recited still encompass homologous variants of the splice variant of an ErbB ligand; specifically, these homologous variants share 90% homology in the N-terminal flanking sequence preceding the cycteine 1 in the EGF domain of a known ErbB ligand. However, Applicant has not provided adequate written description for the genus of the polypeptide that contains the N-terminal variant

sequences. Although claim 1 limits the splice variants by reciting the specific SEQ ID NOs, the claim language "*an isolated polypeptide comprising a splice variant of an ErbB ligand*" reads on additional sequences can be added to the splice variant. Depending claim 10 specifically requires that these additional sequences include "*the N-terminal flanking sequences preceding the cysteine 1 that are at least 90% homologous to the same sequence in the EGF domain of a known ErbB ligand*". The specification does not teach examples of such N-terminal flanking sequences that are at least 90% homologous to any known ErbB ligand. There is no adequate description regarding how long the sequences are, where the changes can be made, or which portion of an ErbB ligand they correspond to. Obviously, in the absence of more information with regard to the nucleic acid or amino acid sequences, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

Therefore, the claims do not meet the written description provision of 35 U.S.C. §112, first paragraph as the specification fails to provide sufficient written description for a polypeptide comprising a splice variant of an ErbB ligand set forth in SEQ ID NO: 81, wherein the polypeptide contains an N-terminal flanking sequence preceding the cysteine 1 that is at least 90% homologous to the same sequence in the EGF domain of a known ErbB ligand. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1, 4, 8-14, 32 and 41 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons set forth previously and the following.

Applicant argues that the claim amendment (limitation to specific sequences 74-84, 93, 95-104 and 109-110) overcomes the enablement rejection. Applicant argues that there is no difficulty making the polypeptides of specified sequences by conventional recombinant DNA techniques. With respect to the "how-to-use" problem, Applicant argues that the present application relates to novel ErbB ligand splice variants that each comprises at least one altered component of the EGF domain that affects ligand-mediated ErbB receptor activation. Applicant argues that it is mentioned that one of the possible mechanisms by which the variant EGF domain affects receptor activation is indirectly by means of ligand sequestration (by binding to an ErbB ligand, thus sequestering it from receptor-dependent activation). Applicant argues that the experimental results shown in the specification provide evidence in support of an inhibitory activity of the splice variants through ligand sequestration. Applicant argues that the disclosure provides objective evidence that splice variants of the invention have the activity/function that is attributed to them, and enables their use.

Applicants' argument has been fully considered but has not been found to be persuasive.

As discussed above, the claims as recited encompass polypeptides comprising a splice variant of an ErbB ligand set forth in SEQ ID NO: 81, wherein the polypeptide has

an N-terminal flanking sequence preceding the cysteine 1 that is at least 90% homologous to the same sequence in the EGF domain of a known EbrB ligand. However, Applicant has not provided sufficient teachings regarding the detailed chemical structure of the encompassed polypeptides, in particular, the N-terminal flanking sequences; for example, how long the N-terminal flanking sequences can be, or which portion of an ErbB ligand they correspond to. Further, there is no guidance regarding where the changes can be made, such that the molecules maintain the functional activities (i.e., binding and inhibitory activity to at least one member of the ErbB/EGF receptor family). In the absence of the detailed structural information for the genus of molecules, one of an ordinary skill in the art would not know how to make the polypeptides as claimed. Further, without the teachings regarding the correlation of structure to function, a skilled artisan has to screen a large number of polypeptides with N-terminal sequence variations and determine their activity as an ErbB receptor antagonist. It would require tremendous undue experimentation, and does not satisfy the enablement requirement of 35 U.S.C. 112, first paragraph that stipulates one of ordinary skill in the art to make and use the invention, rather than “make and test”.

Due to the large quantity of experimentation necessary to generate a large number of the splicing variant polypeptides recited in the claims, and determine their activity/function and usefulness, the lack of direction/guidance presented in the specification, the absence of working examples, the complex nature of the invention, the state of the art which fails to provide compensatory guidance, and the breadth of the

claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

## *Conclusion*

NO CLAIM IS ALLOWED.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
December 29, 2010

/Elizabeth C. Kemmerer/
Elizabeth C. Kemmerer, Ph.D.
Primary Examiner, Art Unit 1646